



Pharmacia & Upjohn

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16 April, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 99D-0121

Draft Guidance for Industry on Waiver of In Vivo
Bioavailability and Bioequivalence Studies for
Immediate Release Solid Oral Dosage Forms
Containing Certain Active Moieties/Active
Ingredients Based on a Biopharmaceutics
Classification System

Dear Sir/Madam,

We thank the FDA for the opportunity to review this draft Guidance for Industry (Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System). We support the efforts evident in this guideline to base regulatory guidances on sound scientific principles. In that regard, however, we have a concern with this proposal. In particular, it is our position that in-vitro dissolution is not a suitable surrogate for in vivo bioequivalence evaluation of marketing applications. More specifically, we do not believe it is appropriate to approve ANDAs for solid oral dosage forms with no human data.

Our concern stems from the principal argument presented in the draft guidance. That is, the statement "a suitable in vitro/in vivo correlation can be assumed for a rapidly dissolving drug product of a highly soluble and highly permeable drug substance, as long as its inactive ingredients do not significantly affect absorption of the active ingredients." On the contrary, we believe that in-vivo/in-vitro correlations are not common for immediate release dosage forms, in general, and in particular, for highly soluble drugs.

99D-0121

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Rather, the applicability and usefulness of in-vivo/in-vitro correlations applies to dissolution rate limited situations, such as extended release dosage forms or poorly soluble drugs in immediate release dosage forms.

This view is also consistent with that of the authors of reference 3 in the draft guidance (Amidon et. al.). They state on p. 417 that “For immediate release dosage forms that dissolve very rapidly, the absorption rate will be controlled by the gastric emptying rate and no correlation with dissolution is expected.”

Beyond this fundamental issue, we have several specific comments regarding the proposed guidance:

Section II, Last paragraph.

As noted above, the draft guidance states that “a suitable in vitro/in vivo correlation can be assumed for a rapidly dissolving drug product of a highly soluble and highly permeable drug substance, as long as its inactive ingredients do not significantly affect absorption of the active ingredients.” We believe that this is misstated. Reference 3 in the Draft Guidance indicates that there should be a correlation only if the dissolution rate is slower than the gastric emptying rate, otherwise there will be limited or no correlation.

Section III.C.

We do not understand the reason why a pH 4.5 buffer has been specified for determining that a drug product is rapidly dissolving.

Section IV.A.

We believe that the potential for errors in pH determination exist within the document as written, especially for highly soluble salts of poorly soluble weak acids or bases. These salts can self-buffer and overwhelm the buffer capacity of the media used for the determination, resulting in equilibrium pH values which are different from the original buffer pH. Unless the pH is repeatedly checked and adjusted after equilibrium is achieved, it is possible to substantially overestimate the solubility of the drug at a given pH.

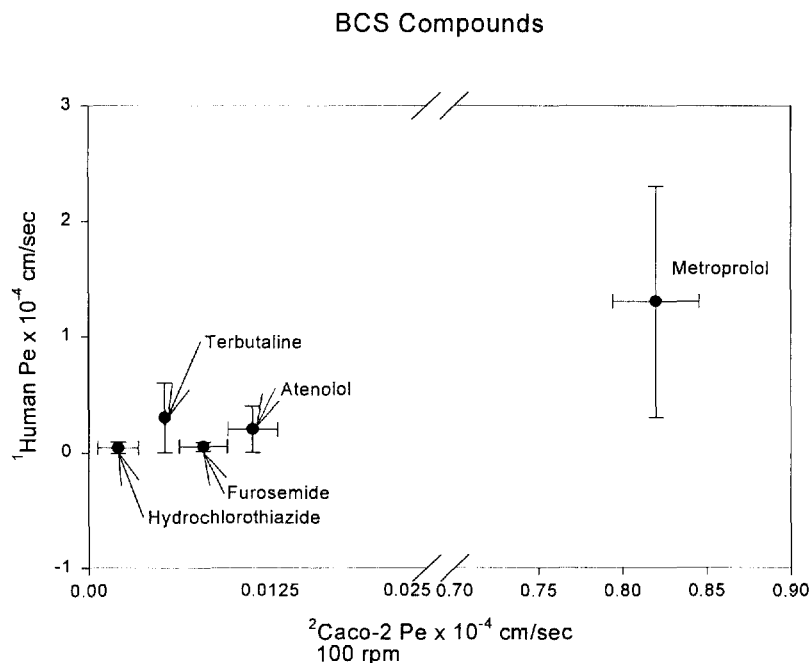
Section IV.B.2.

In the first paragraph, the wording stipulates that an acceptable method for measuring in vitro permeability will consist of “a monolayer of cultured human intestinal cells”. This is a departure from the recommendations of the 1998 workshop on permeability definitions that was jointly sponsored by the FDA and AAPS. Since the draft guideline requires characterization of the surrogate model with respect to human permeability, and applies only to passively absorbed drugs, it is not necessary to mandate that human cells are the only acceptable model. Several other cultured cell models serving this purpose are available, and have been described in the literature. Notable among these is the MDCK (a canine kidney cell line) which gives qualitatively identical and quantitatively similar results to Caco-2, the human cell preferred model. Additionally, since

Navicyte owns the licensing rights to Caco-2 cells, it does not seem appropriate for an FDA Guidance to require the pharmaceutical industry to do business with a specific vendor.

We agree with the strategy that two well-characterized model drugs should be used as internal standards for permeability determinations. However, it may be possible to choose “standards” which skew the results in favor of high permeabilities.

A related concern regarding the selection of reference and/or standard compounds is the requirement that they be from the group for which human permeability values have been obtained. Lennernas and Amidon are presently the only sources of such data. It may be appropriate to have the values confirmed in another laboratory. Further, the standard errors associated with these measurements (cf Winiwarter, S., Bonham, N.M., Ax, F., Hallberg, A., Lennernas, H., and Karlen, A., “Correlation of human jejunal permeability (*in Vivo*) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach”, J. Med. Chem., 41 (1998) 4939-4949.) suggests that the rank order based on the means is questionable. This issue may become important when trying to establish a correlation with a method exhibiting much less standard error. Regarding standard selection, the data shown in the figure below demonstrate considerable overlap in the human data for the permeabilities of terbutaline and atenolol (considered low permeability) with metoprolol (a candidate high permeability standard). An applicant might be tempted to argue that terbutaline or atenolol are appropriate for use as high-permeability standards in the Caco-2 model.



Section VII.A.

Although we recognize that the language in the Draft Guidance is taken directly from 21 CFR 320.23 (d)(2), we question the appropriateness of using a suspension as a reference for determining bioavailability. A suspension cannot necessarily be assumed to be rapidly dissolving.

We thank you for the opportunity to comment on this draft guidance. Please let us know if you have any questions.

Sincerely,

Pharmacia & Upjohn, Inc.

A handwritten signature in black ink, appearing to read "Dan T. Fagan", followed by a horizontal line.

Dan T. Fagan

cc: Ken King, John Landis

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